

REMARKS

In the Final Action dated January 22, 2010, claims 1, 2, 5-16, 18-23 and 26-30 were pending. Claims 8, 9, 13-16, 20-22 and 27-29 were withdrawn from consideration, and claims 1, 2, 5-7, 10-12, 18, 19, 23, 26 and 30 were under consideration and rejected. Applicants' Response filed under 37 C.F.R. §1.116 on July 22, 2010 was indicated as "entered" in the Advisory Action dated August 6, 2010, and warrants entry of record in view of the Request for Continued Examination submitted herewith in any event.

Applicants have further amended the claims in the instant Response. Claims 23 and 26 are cancelled herein. Claims 61-71 have been added and claims 1, 2, 5, 10, 18 and 30 are amended herein. Specifically, independent claims 1 and 2 have been amended to define the antagonist as follistatin, as supported by the specification and original claim 26. New claims 61 and 71 further define follistatin as follistatin 288 or follistatin 315, as supported by the specification, e.g., page 34, line 30 to page 35, line 7. Claims 5, 10, 18 and 30 have been amended to delete the reference to claim 2, and delineate the relevant subject matter in new claims 62-70. No new matter is introduced by these amendments. Applicants reserve the rights to pursue the subject matter encompassed by the original claims in a continuation application.

Upon entry of the instant Response, claims 1, 2, 5-16, 18-22 and 27-30 will be pending, and claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 will be under consideration as directed to the elected subject matter, i.e., a method of downregulating activin functional activity by introducing an activin antagonist wherein the antagonist is follistatin and wherein the specific condition is airway inflammation, an acute inflammatory response and targeting activin A. Reconsideration of the claims presented herein is respectfully requested in view of the amendments made and the following remarks.

The Examiner has rejected claims 1, 2, 5-7, 10-12, 18, 19 and 30 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent Publication 2003/0162715 (hereinafter "the '715 publication"). The '715 publication allegedly discloses follistatin-like-3 protein to treat disease. Although the Examiner agreed with Applicants that follistatin-like-3 is different from follistatin

in the present application, the Examiner states that because the claims of the present application were broadly drawn to any activin antagonist and because follistatin-3 appears to bind to activin in a dose-dependent manner, the '715 publication anticipates the present application.

Applicants, however, submit that independent claims 1 and 2 have been amended herein to recite treatment of a mammal with follistatin rather than with an activin antagonist generally; thus, Applicants respectfully submit that the '715 publication drawn to follistatin-like-3 protein does not anticipate the presently claimed invention. Applicants respectfully request that the rejection of pending claims 1, 2, 5-7, 10-12, 18, 19 and 30 under 35 U.S.C. §102(b) as being anticipated by the '715 publication be withdrawn.

The Examiner has also rejected claims 1, 2, 5-7, 10-12, 18, 19 and 30 under 35 U.S.C. §102(b) as allegedly anticipated by WO 03/006006057 (hereinafter "the '057 publication"). As Applicants have argued previously, fibrosis may occur subsequent to an inflammatory response but fibrosis is not the inflammatory response itself. Fibrosis, instead, is a form of scarring. The fact that inflammation and fibrosis may occur sequentially is irrelevant to the treatment of inflammation. Moreover, even if fibrosis is successfully treated in a subject – *i.e.*, the scarring is prevented – this result is not necessarily achieved via down-regulation of an inflammatory response.

The Examiner states that the '057 publication teaches use of follistatin in the treatment of diseases associated with fibrosis such as interstitial lung disease, which is airway inflammation. Applicants do not dispute that fibrosis can occur after an inflammatory response, as is the case with interstitial lung disease where an inflammatory response ultimately leads to development of fibrotic tissue. However, follistatin in the context of the '057 publication is taught to be used to modulate fibrotic processes, not inflammatory processes. Although the diseases which are listed at page 3, lines 30-33 of the '057 publication mention inflammatory fibrotic diseases, the fact is that the disclosure is directed to treating the fibrotic processes – scarring – not the inflammatory aspects of these diseases. There is no teaching in the '057 publication of modulation of the inflammatory response, such as an inflammatory response which does not lead to a fibrotic outcome; rather, the '057 publication is directed to the cellular events of fibrosis, which occur

separately from and subsequently to the earlier inflammatory response.

As argued previously, the effects of the inflammatory cytokine cascade are critical to the management of, *e.g.*, septicemia, which kills patients well before a fibrotic response commences. In a reference cited previously by Applicants, mice died within twenty-four hours of an LPS challenge, well before the fibrotic response could occur. As taught by the present application, follistatin can prevent this mortality by downregulating the inflammatory response. In contrast, the '057 publication teaches that in any condition where fibrosis occurs, irrespective of whether it is preceded by an inflammatory response, follistatin can be used to down regulate the fibrotic events. This is markedly different to that which is claimed in the present application wherein one can modulate an inflammatory response irrespective of whether or not fibrosis occurs. The '057 publication teaches that where a fibrotic outcome is associated with an inflammatory condition, the tissue scarring aspect can be down-regulated; however, the preceding inflammatory response will still occur. The fact that the '057 publication teaches that follistatin can down regulate fibroblast stimulation does not teach anything about the regulation of inflammatory responses. Thus, because many inflammatory responses are not associated with fibrosis, and fibrosis occurs at a later time point to inflammation, the '057 publication is distinguished from does not anticipate the claimed invention. Withdrawal of the rejection based on the '057 publication is therefore respectfully requested.

Claims 1, 2, 5-6, 10-11, 18, 19, and 30 have also been rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 8911862 (hereinafter "the '862 publication"). The Examiner alleges that the '862 publication teaches that inhibin is useful in wound healing, autoimmune disease, immunodeficiency disease, transplant rejection and infection. Applicants respectfully submit that independent claims 1 and 2 have been amended herein to recite treatment of a mammal with follistatin rather than with an activin antagonist generally; thus, Applicants respectfully contend that the '862 publication does not anticipate the present invention. Applicants respectfully request that the rejection of pending claims 1, 2, 5-7, 10-11, 18, 19 and 30 under 35 U.S.C. §102(b) as being anticipated by the '862 publication be withdrawn.

The Examiner has rejected Claims 1, 2, 5-7,10-12, 18, 19 and 30 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent Publication 2002/0192216 (hereinafter 'the '216 publication). The '216 publication discloses that follistatin is an inhibitor of the Hedgehog signaling pathway. As Applicants have argued previously, the Hedgehog signaling pathway does not include activin and it is therefore not entirely clear how this prior art reference is relevant to the claimed invention. Inflammation is an extremely complex process which involves multiple signaling pathways. Hedgehog plays a role in this context but is a different and distinct pathway to that which has been identified in the context of the present invention. The fact that the present inventors have determined that activin is a crucial molecule in terms of the inflammatory cytokine cascade provides an alternative means of treating inflammatory conditions based on antagonizing activin.

Hedgehog is an intracellular signaling molecule. Activin is not an intracellular signaling molecule. The '216 publication is based on binding a molecule to the cell surface which sends a signal internally to down regulate Hedgehog signaling intracellularly or, presumably, to use a molecule that can be internalized by a cell in order to down regulate Hedgehog signaling. Activin is not an intracellular signaling molecule and one skilled in the art would not assume that any molecule which can down regulate intracellular signaling would necessarily have any role in terms of down regulating extracellular cytokine functionality as a means to down regulate the cytokine cascade which underpins the inflammatory response. The cytokine cascade is not an intracellular mechanism. In fact, a molecule that is shown to impact intracellular signaling is one that binds to or is internalized by a cell. Such an understanding would not lead one to conclude that a molecule that impacts intracellular signaling would act as an antagonist of an extracellular cytokine, especially one that plays no evident role in the signaling pathway. Additionally, cytokines, such as follistatin, are pleiotropic. The fact that follistatin may be shown to down regulate Hedgehog which therefore down regulates Hedgehog signaling and prevents production of BMP, does not inherently teach that which is claimed in the present application, *i.e.*, that activin is in fact the crucial cytokine that regulates the inflammatory response and that antagonizing activin will achieve an effective anti-inflammatory response.

The '216 publication discloses that follistatin is an inhibitor of an intracellular signaling pathway, but provides absolutely no disclosure or teaching of the role of follistatin in the context of regulating the extracellular cytokine cascade via regulation of extracellular protein molecules, such as activin, or that follistatin actually has an impact on inflammation. In short, the '216 publication does not provide an enabling disclosure that would anticipate the claimed invention. A prior art reference must provide an enabling disclosure of the subject matter of the claim(s) against which it is cited. *Elan Pharm., Inc., v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. *Id.* Clearly the '216 publication is not enabling, at least as far as follistatin is concerned; accordingly, the '216 publication does not anticipate the subject matter of the claimed invention.

The Examiner has rejected Claims 1, 2, 5-7, 10-12, 18, 19 and 30 under 35 U.S.C. §112, first paragraph, as failing to evidence possession of the claimed invention at the time of filing the application. Specifically, the Examiner alleges that there is no written description for "an activin antagonist" wherein the antagonist is a "proteinaceous molecule." Applicants submit that independent claims 1 and 2 have been amended herein to recite treatment of a mammal with follistatin rather than with "an activin antagonist" generally; thus, Applicants respectfully contend that this amendment obviates the rejection under 35 U.S.C. §112, first paragraph in relation to recitation of "an activin antagonist." Moreover, claim 23, relating to proteinaceous and non-proteinaceous molecules, is cancelled herein thereby obviating this rejection as well. Thus, Applicants respectfully request that the rejection of pending claims 1, 2, 5-7, 10-12, 18, 19 and 30 under 35 U.S.C. §112, first paragraph, be withdrawn.

In view of the foregoing amendments and remarks, Applicants aver that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to be 'XZ' followed by a long horizontal stroke.

Xiaochun Zhu

Registration No. 56,311

Scully, Scott, Murphy & Presser, P. C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
(516) 742-4343
XZ:eb